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10/551,840	01/20/2006	Fabrizio Samaritani	7541-6	4228

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WOODARD, EMHARDT, MORIARTY, MCNETT & HENRY LLP
111 MONUMENT CIRCLE, SUITE 3700
INDIANAPOLIS, IN 46204-5137

EXAMINER	
GUPTA, ANISH	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
10/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,840	SAMARITANI ET AL.	
	Examiner	Art Unit	
	ANISH GUPTA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-49,51-53,56-64,72-80,82-89,189-193,195-201 and 203-215* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-49,51-53,56-64,72-80,82-89,189-193,195-201 and 203-215* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed July 15, 2008 is acknowledged. Claims 212-215 were added. Claims 46, 72, 73, 74, 79-80, 86, and 198 were amended. Claims 50, 194 and 202 were canceled. Claims 46-49, 51-53, 56-64, 72-80, 82-89, 189-193, 195-201, and 203-215 are pending in this application.

2. All rejections made in the previous office action and not cited herein are hereby withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 46-49, 51-53, 56-64 198-201, and 203-215 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffman et al. (US2002/0165146).

The claims are drawn to a formulation cresol, FSH and a surfactant selected form poloxamer 188, poloxamer 217, poloxamer 237, poloxamer 238.

The reference teaches a formulation comprising FSH. Specifically, the reference discloses formulation of FSH with cresol or phenol (see page 27, claim 1). The reference also states that that FSH is in a concentration between 5.0 micorgrams/ml to 2 milligram/ml (See page 11, paragraph [0097]). The cresol is in the concentration of 23 millimolar to 35 millimolar (see page 11, para [0098]). The reference also disclose that other additives such as tween 20, and pluronic F68, poloxamer 184 or 188 can be added to reduce aggregation (see page 12, para [100]). The reference discloses the use of isotonicity agents such as sucrose and methionine (see paragraph [0046]). The pH of the formulation is between 6.8 and 7.8 (see page 11, para [0099]). The reference states that the FSH can be recombinently produced and can be from urinary sources (see page 10, para [0094]). While the reference does not specifically teach a formulation with cresol, FSH and poloxamer, it would have been obvious to add poloxmer 184 or 188 to a formulation of cresol and FSH so as to prevent reduced aggregation.

As for the dosages claimed, the MPEP states "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. . . .The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." See MPEP 2144.05. Here, the reference disclose the use of various concentrations for the FSH and cresol. It would have been obvious to optimize the optimum dosage for each component.

Response to Arguments

Applicants argue that Hoffman recites the use of Tween 20, etc. in FSH formulations. However, the reference disclose numerous other excipients and "fails to provide an enabling disclosure for such combinations, which range in the millions. . .A person of ordinary in the art would not understand Hoffman as teaching the viability of each of the vast numbers of combinations which could be theorized form the disclosure." The disclosure of the solubilizers are a mere "laundry list" without any suggestion as to which would work in a given formulation. The examples in the reference do not recite the use of some of solubilizers disclosed. Applicants assert that FSH is known to be especially susceptible to the deleterious effects of excipients and the effects are not straightforward. It is clear from the state of the art "that the preparation of stable FSH formulation was known to be difficult proposition, with essentially any change or addition as to excepient(s) having the potential of resulting instability."

Furthermore, Hoffmann, while teaching solublizers as an optional excipient with the specific purpose being "to reduce aggregation, the results in the instant application indicate that TWEEN 20 resulted in turbid or milky solutions. "This result demonstrates the lack of predictability for stability of protein formulations, and confirms the lack of a meaningful teaching by references such as the cited Hoffman application when lengthy lists of theoretical excipients are recited. This is also in distinct contrast to the suggestion in the cited Skrabanja patent, which states that Tween 20 is "especially preferred" for use in its FSH formulations." Finally, Applicants state that the newly added claims add the transitional term "consisting essentially of."

Applicants arguments have been fully considered but have not been found persuasive.

First, Applicants state that the different combinations generally taught by Hoffmann et al. are not enabled. Presumably, the non-enablement is established by Maa et al. which teaches that

phenolic compounds "have 'adverse effects when added to protein formulations." However, as Applicants probably, know that "[w]hen the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability." See MPEP 2121. The reference of Maa et al. is insufficient to show non-enablement. The reference uses rhGH and never discloses the use of FSH. Thus, it unclear how the teachings of Maa can be used to establish non-enablement for Hoffmann. Further, if the premise of non-enablement is based on the number of formulations encompassed by the reference and the lack of working examples, Applicants are reminded that lack of working examples is never the sole reason for questioning enablement. See MPEP 2164.01(c). Since Applicants have not presented any evidence to establish that the reference is non-enabling, such arguments have not been found persuasive. Finally, it should be noted that the instant claims recite that the formulation can contain a "diluent." The specification states that diluent refers to sugars, buffers, salts, short chain organic alcohols, and short chain ketones. However, Applicant specification fails to provide specific examples of formulations that use different ketones or sugars. Simply put, Applicants would not acquiesce to an enablement rejection merely because the instant specification fails to provide examples for all possible combinations with diluent. Accordingly, the reference cited is wholly enabled.

Furthermore, it seems that Applicants are arguing that the prior art does not use the solubilizing agent for the same reason as the claimed invention. However, "[t]he reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the

combination to achieve the same advantage or result discovered by applicant." See MPEP 2144. Here, the prior art teaches the use of tween 20, and pluronic F68, poloxamer 184 or 188 can be added to reduce aggregation. One would be motivated to use any and all solubilizing agents outlined by the reference for that purpose.

Moreover, Applicants imply that Tween is "especially preferred." However, Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. See MPEP 2123. Finally, Applicants state that the newly added claims have transitional language of "consisting essentially of." The MPEP states "[f]or the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising."" Since the specification does not clearly set forth a clear indication in the specification or claims of what the basic and novel characteristics actually are, the claims have been interpreted as comprising.

Rejection is maintained.

4. Claims 72-80, 82-89, 189-193, 195-197 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffman et al. as applied to claims 46-49, 51-53, 56-64 198-201, and 203-215 above, and further in view of Skrabanja et al. (US 5929028).

The claims are drawn to a formulation cresol, FSH and a surfactant selected form poloxamer 188, poloxamer 217, poloxamer 237, poloxamer 238.

The reference of Hoffman et al. has been discussed supra. The reference implies that FSH can be used alone or in combination with other gonadotropins (see page 3, paragraph [0028]). The

difference between the US pg pub and the instant application is that the US pg pub doe not disclose the use of LH.

However, Skrabanja et al. teaches that combination of FSH with LH has been used to stimulate ovarian growth (see col. 1, lines 15-30). The reference specifically teaches formulations of FSH and LH (see col. 6). The reference disclose both liquid formulation of liquid formulations that can be freeze dried (see col. 6). The reference disclose that the formulations can have numerous additives such as sucrose (col. 5, lines 1-15) and non ionic surfactant such tween 20 or pluronic f123 (see col. 5, lines 23-34). It would have been obvious, therefore, to use a combination of FSH and LH because the combination formulation has been used for stimulation of ovarian growth. There would have been a reasonable expectation of success because the Skrabanja et al. teach many of the same components in a formulation comprising LH and FSH as taught in Hoffman. Furthermore, Hoffman implies that the FSH their invention can be used in combination with other gonadotropins.

Response to Arguments

Applicants assert that the claimed invention "solves the problem of precipitations and provides 'clear solutions' which are free of visible particles, thereby providing 'a stable formlulation that avoids the problems of precipitation in the presence of a bacteriostatic agent, such as m-cresol and phenol." The secondary reference of Skranbanja et al. teaches the difficulties of preparing stable protein formulations. The reference does not teach any formulations including an anti-microbial agent.

Applicants assert that the combination of the references "would not be within the ordinary meaning skill in the art" because Skrabanja et al. describes the use of surfactants as anti-absorption agents and prevent loss of gonadotropins as a result of absorption of the protein to the walls of the

container. Hoffman only disclose the sue of solubilizers in order to reduce aggregation. Furthermore, one could "not predict the effect caused by additional present of the LH" since Hoffman only discloses FSH." Applicants make reference to all of the different agents utilized by both Hoffman and Skrabanja.

Applicants arguments have been fully considered but have not been found persuasive.

The mere fact that Skranbanja et al. uses the surfactant for a different purpose than Hoffman is not a basis for non-obviousness. The rejection has been set up to such that the primary reference is modified to use LH in combination with FSH. The combination of FSH with LH has been used to stimulate ovarian growth. The primary reference disclose the use of FSH for fertility disorders. Thus, it would have been obvious, therefore, to use a combination of FSH and LH because the combination formulation has been used for stimulation of ovarian growth. The combination would result in a reasonable expectation of success. Since the secondary reference uses similar non-ionic surfactants, non only would the surfactants result in less aggregation but also prevent absorption of the protein. Applicants seem to be looking for the rejection to establish absolute predictability of success. However, "[o]bviousness does not require absolute predictability of success." See MPEP 2143. All that is required is that there be reasonable expectation of success. Given the teachings of the art and the fact that the primary reference teaches that the FSH can be used in combination with at least one additional gonadotropin, there is a reasonable expectation of success.

Rejection is maintained.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can normally be reached on (571) 272-0562. The fax phone number of this group is (571)-273-8300.

/Anish Gupta/

Primary Examiner, Art Unit 1654